Myasthenia Gravis mimics: An audit of cases identified at Groote Schuur Hospital over 20 years

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Abstract

Background: Myasthenia gravis (MG) is characterised by fatigable muscle weakness. The diagnosis is made clinically and supported by ancillary tests such as electrophysiological studies, autoantibodies and pharmacological responses. Autoimmune MG will respond to immune therapy. Although there are several case reports of patients who were incorrectly diagnosed as MG, this study describes the MG mimics encountered at Groote Schuur Hospital, Cape Town, over a period of 20 years.

Aims & Methods: To describe the MG mimics captured in the MG database (1996 to 2017) by final diagnosis, the age at symptom onset, the time delay and clues which led to the final diagnosis.

Results: There were 31 cases identified; 10 were probable congenital myasthenic syndromes (CMS), 6 functional neurological symptoms (FNS), 6 motor neuron disease (MND) variants, 3 mitochondrial cytopathies, 4 had definite or probable muscular dystrophy (MD), 1 progressive supranuclear palsy and 1 with a multiple sclerosis brainstem relapse. Median age at symptom onset was 10 years for CMS, 18 for mitochondrial cytopathies, 53 for FNS, 58 for the muscular dystrophy cases and 63 years for those with MND. The median time delay between the false "MG" diagnoses to the reviewed diagnosis, which also corresponds to the time on immunotherapies, was 45 months in CMS, 48 months in mitochondrial cytopathy, 4 in MND, and less than 3 months in FNS, MD, PSP and MS.

The most important factor for reviewing the diagnosis was treatment unresponsiveness to immune therapy. Some of the CMS and mitochondrial cytopathy cases were treated with immune therapies for many years, without responsiveness, before referral to our centre. Additional features for CMS were childhood onset, family history of similar symptoms and, although no response to immune therapies, they responded to pyridostigmine +/- salbutamol. Mitochondrial cytopathies had long duration of symptoms and the diagnosis was confirmed by mitochondrial DNA deletion detection. MND patients showed disease progression within a few weeks despite some transient improvement with anticholinesterases. The FNS diagnoses were based on signs which were inconsistent and symptoms resolved after psychotherapy. Two MD cases (myotonic muscular dystrophy and probable oculopharyngeal muscular dystrophy, respectively) presented with respiratory failure, and could not be weaned off invasive ventilation.

Conclusion: The main points are that, not all patients with ptosis and fatigable symptoms have myasthenia gravis. Non-responsiveness to immune therapies should raise suspicion of an alternative diagnosis and prompt referral to a specialist clinic. Transient modest improvement in bulbar and limb muscle symptoms have been observed in patients with early manifestations of motor neuron disease.

Introduction and literature review

Myasthenia gravis (MG) is a treatable immune-mediated neuromuscular disorder that is characterised by fatigable weakness involving specific muscle groups.[1, 2] Fluctuating fatigable muscle weakness is the hallmark for MG diagnosis.[2,3,4] Specific muscles groups involved may be ocular, bulbar, axial and proximal limb muscles.[3] MG usually presents with fluctuating ptosis with or without diplopia due to ocular muscle weakness. In about 60% of MG patients, ptosis with/ without diplopia is the initial presentation and often starts asymmetrically but can also be symmetrical at onset.[2, 3,5] In about 15% to 20% of patients, the disease is confined to ocular muscles after 2 years of symptom onset[4,6] and this is called ocular MG (OMG). However, in most patients presenting with ocular manifestations, the disease progresses to other muscle groups within 2 years of onset [2] and then referred to as generalised MG (GMG). Here the symptoms may include dysarthria and dysphagia due to bulbar muscle weakness, facial weakness, proximal limb or axial muscle weakness with/ without dyspnoea due to respiratory muscle weakness. MG occurs at any age and is usually influenced by age and sex.[2] In acetylcholine receptor (AChR) antibody (AChR-Ab) positive myasthenia gravis manifesting before middle age, women are more frequently affected than men, [2] whereas in older patients men may be more frequently affected.[2, 5] The incidence of MG in South Africa is comparable to the rest of the world.[1]

The diagnosis of MG is made based on the clinical presentation as described above and supported by ancillary tests which include bedside tests such as 1) ice packs that are put over the patient's closed eyelid which has a cooling effect on cholinesterase enzyme stability that results in a transient improvement of ptosis, 2) oral pyridostigmine or intramuscular neostigmine, anticholinesterase inhibitors that inhibit the acetylcholine from being broken down, resulting in temporal improvement of symptoms; 3) electrophysiological tests such as repetitive nerve stimulation (RNS) showing decremental responses in the compound motor action potential (CMAP) of >10% at 2-3 Hz stimulation[7] or single fibre electromyography (SFEMG) showing increased jitter; and 4) detection of autoantibodies in the blood which target muscle endplate proteins.[4] In some cases with the classical clinical picture of fatigable muscle weakness, in whom all tests are negative, we use clinical response to immunosuppressive treatment to support the diagnosis of MG.

In most cases, MG is caused by autoantibodies directed towards nicotinic AChR found at the postsynaptic neuromuscular junction.[2, 6] However there are other proteins at the postsynaptic junction such as muscle specific tyrosine kinase (MuSK) and lipoprotein receptor related protein 4 (LRP4) that might also serve as a target for the autoimmune attack. These proteins induce clustering of AChRs and are important in maintaining the neuromuscular junction.[2, 6] About 85 to 90% of MG patients have AChR antibodies detected by the radioimmunoprecipitation assay (RIA) method in the sera but 15% will be negative. Some of these patients can have the other antibodies such as the anti-MuSK or anti-LRP4 antibodies. Using a cell based assay method, clustered AChR antibodies were detected in up to 50% of patients who were negative for AChR and MuSK antibodies using RIA. Despite using both RIA and CBA methods to detect autoantibodies, a small proportion of patients will remain negative on these tests.[7]

Although RNS is the most widely used electrophysiological test to support the diagnosis of MG, the sensitivity is about 70% when proximal muscles are investigated. This value decreases even further in mild generalised MG.[8, 9] In OMG, the sensitivity of RNS is even lower (<30%).[8,9] This means that about 30% of patients with GMG and 70% of patients with OMG would be falsely negative. Furthermore, under certain conditions RNS can be falsely positive, although rarely.[10] SFEMG is the most sensitive and specific electrophysiological test in diagnosing MG, [8] but this is not widely available in most centres in the developing world mainly because it is time-consuming.

MG mimics are conditions that may present like MG, but over time it becomes apparent that the diagnosis is incorrect. These patients may be exposed to several immune therapies before an alternative diagnosis is considered. On the other hand, MG is a treatable disease that should not be missed.

Briefly, there have been several published case reports describing conditions that mimic MG. Those conditions include, thyroid ophthalmopathy,[11] Guillain-Barre syndrome,[12] chronic progressive external ophthalmoplegia (CPEO),[13] movement disorders,[14] motor neuron disease,[15] brainstem tumors,[16-19] and structural intracranial lesions such as aneurysms,[20,21] Chiari malformations[22] and Dandy walker syndrome.[23] There are also case reports of drug induced MG in patients treated with penicillamine[24] and statins[25] although these are not strictly MG mimics. Myasthenic syndromes such Lambert Eaton myasthenic syndrome,[26] and congenital myasthenic syndrome[27]can be confused with autoimmune MG. Muscular dystrophies such as myotonic dystrophy and oculopharyngeal dystrophy,[26] may be misdiagnosed. Another mimic would be generalised fatigue[28] which can be confused with weakness.

Despite several case reports on MG mimics, there are only a few case series. The first study from Boston, described 130 patients that were seen between 1954 to 1964 with an initially diagnoses of MG.[28] These patients were later reclassified to alternative diagnosis such as chronic fatigue, which was the commonest mimicker of MG accounting for 38% of the sample.[28] Other diagnoses included ocular or generalised myopathies (22%), thyrotoxicosis (8%), brain stem disorders (8%), extrapyramidal disorders (9%) as well as other miscellaneous diagnoses in 17%.[28]

Moorthy et al, described 8 patients with an initial diagnosis of MG, in whom a structural intracranial lesion such as parasellar tumor or aneurysm was identified, either as a mimic or co-occurring with MG.[29]

Garg et al. analysed the Australian cohort of 25 patients with seronegative MG of whom 7 (4%) were found to have genetically confirmed CMS.[27] Some of the clues that led to this diagnosis apart from negative antibodies to the most common antigens in MG were, a positive family history, lack of response to CHEI and a history of childhood onset.[26]

The aim of our study was to describe the MG mimics that have been encountered at Groote Schuur Hospital (GSH), Cape Town, over a period of 20 years. We described them by; final diagnosis, the age at symptom onset, time delay before final diagnosis and clues that led to the final diagnosis.

Methods

This was a description of the GSH Neurology unit MG database. All patients diagnosed with MG by our department or referred as such from elsewhere and who received treatment for MG are entered into the database. The database is compiled as a hand written register during the clinic and information is entered electronic on 6 monthly basis. Observational data were collected prospectively by Prof JM Heckmann, who also reviewed the patients personally, between January 1996 to December 2017.

When the diagnosis of MG was reviewed and an alternate diagnosis was recorded, the data entries were flagged. All patients identified were included in the cohort. Information collected included final diagnosis, age at onset, age at final diagnosis, time delay before final diagnosis as well as the duration of symptoms prior to the false MG diagnosis. In addition, I reviewed from the folders the investigations which 'supported' the initial diagnosis of MG (such as RNS, autoantibodies, oral/intramuscular (IMI) anticholinesterase inhibitors (ChEI)), clues that led to the final diagnosis and how it was made, and investigations that supported the final diagnosis. Where information was missing from the database, I reviewed the patients' folders and filled in the gaps.

Ethical consideration

The study was approved by the Human Research Ethics Committee, Faculty of Health Sciences, and University of Cape Town (HREC: 670/2017).

Data analysis

Data were analysed in Microsoft excel. Continuous data with skewed distribution is expressed as median and interquartile range (IQR). Proportions of subgroups by final diagnosis were expressed in percentages (%).

Results

31 cases were identified and classified in to seven groups of MG mimics as shown in table 1. These were; 10 (32%) with probable congenital myasthenic syndromes (CMS), 6 (19%) with functional neurological disorders (FuD), 6 (19%) with motor neuron disease (MND), 4 (13%) with muscular dystrophies (MD), 3 (10%) mitochondrial cytopathies (Mito), 1 progressive supranuclear gaze palsy (PSP) and 1 case who was known with relapsing multiple sclerosis (MS) and who developed a brainstem relapse.'

Table 2 outlines the initial clinical presentations and clues that led to the final diagnosis.

A. Probable congenital myasthenic syndromes (CMS) was the most common mimic of MG in our cohort. The median age for onset of symptoms was 10 years although the IQR was from 6 to 20 years (see table 1) The median duration of symptoms to false "MG" diagnosis was 8 years but the final diagnosis was only made after several years. Therefore, most of these cases received immune therapies for more than 3 years before the diagnosis was altered. The median age at 'final' diagnosis was 26 years.

All these patients, except one, presented with bilateral fatigable ptosis. Additional features in those with ptosis were; ophthalmoplegia in three and fatigable limb weakness in three patients. One patient presented only with fatigable limb-girdle weakness at age 12. One patient with long-standing ptosis decompensated at the age 61 developed dysphagia with nasal regurgitation requiring nasogastric feeds for one week. His diagnosis became evident within a few weeks when he failed to respond to a course of intravenous immunoglobulin.

Although we do not have confirmatory genetic testing for these patients they had evidence of a myasthenic syndrome based on the following; 1) objective positive responses to ChEI in 60% (6). However, 40% (4) had no response to ChEI and these included mainly the childhood onset cases with only ptosis (one case was seen by Prof Newsom-Davis (Oxford) who concurred with the clinical diagnosis of CMS); 2) RNS showed reproducible decremental responses with reductions in the CMAPs of 40% (trapezius) in two patients , 36% (abductor digiti minimi) in one, 13% (trapezius) in one and 10% in one patient. Two did not have RNS testing; one young child with ptosis and an adult with childhood onset fatigable ptosis/ophthalmoplegia who declined the testing – neither of them responded to ChEI. Interestingly, the latter patient's parents were consanguineous from Pakistan which could predispose to autosomal recessive genetic disorders.

All patients tested negative for AChR-antibodies, except one who had positive AChR-Ab with titre of 4.8 nmol/L (<0.25nmol/L: Negative) at the age of 72 years. This patient had long standing fatigable ptosis since childhood. The patient underwent eyelid surgery in her '20's. As an elderly adult, the ptosis was picked up incidentally by a neurologist when she consulted him for sensory neuropathic symptoms related to diabetes. Since the ptosis was fatigable, the neurologist tested for AChR-ab which were positive. The patient was managed with prednisone and methotrexate for several years without any benefit although she benefited somewhat from pyridostigmine. Interestingly, her brother also had childhood onset ptosis and was also diagnosed elsewhere with MG.

Table 1 outlines the therapies which these patients received before the reversal of the diagnosis. Six patients received prednisone, two had additional steroid sparing agents (either azathioprine or methotrexate for almost 5 years), one a cyclophosphamide infusion and another two had intravenous immunoglobulin (IVIG). In one patient a thymectomy was performed before he was diagnosed with CMS by our clinic.

These cases have not been molecularly confirmed as CMS. However, we based the diagnosis on childhood onset of fatigable symptoms, a family history in three of our patients, a positive response to either CHEI and/or RNS.

Immunotherapies were discontinued although four patients continued with pyridostigmine and in two salbutamol was added. They all showed good long term responses.

B. Mitochondrial cytopathies due to mitochondrial DNA (mtDNA) deletions accounted for 3 (10%) of the cases. These cases were all molecularly confirmed cases of chronic progressive external ophthalmoplegia (CPEO) with/without additional symptoms/signs. The median age at symptom onset was 18 years. The median duration of symptoms to the false diagnosis of "MG" was 3 years and these cases were receiving immune therapies for a median duration of 4 years before altering the diagnosis. The median age at the final diagnosis was 41 years.

The initial clinical presentation as shown in table 2; was unilateral ptosis for more than a decade in 2 patients before progressing to bilateral ptosis. The neuromuscular disorder progressed with the development of complete external ophthalmoplegia, bulbar symptoms and mild proximal limb weakness over several years. Interestingly, the third patient had asymmetrical ptosis initially with a positive lid curtain sign also known as enhanced ptosis which is seen in MG. The examiner elicits this by elevating the more ptotic eye and a positive result is when the ptosis increases in the contralateral eye. This is explained by Hering's law where by paired ocular muscles receive equal innervation and positive results is highly suggestive of MG.[30]

The ancillary tests which were initially interpreted as supportive of MG by the attending neurologists were mainly the reported subjective positive responses to ChEI in all three patients and the symptoms, although mild, of fatigability. One patient felt her speech and dysphagia had improved about 35%, and the other patient had improvement in muscle strength. One patient showed a non-reproducible decremental response of 12% on the RNS. As expected AChR-Abs were negative in all three cases.

One patient referred herself for a second opinion after living 20 years with a diagnosis of "MG". The diagnosis was reviewed based on the clinical history of no clear response to therapy. Clues that led to revisiting the diagnosis in all three cases can be summarised as a slow progression of the symptoms despite immunotherapy, equivocal fatigability on examination, as well as no clear response to immunotherapy. Two patients had muscle biopsies that showed COX negative fibres and genetic studies confirmed the mtDNA deletion in blood lymphocytes. The third patient had scattered COX negative fibres on the muscle biopsy and a negative mtDNA deletion screen in blood lymphocytes but large-single mtDNA deletion was detected in muscle mtDNA extracted from the muscle biopsy.

C. Functional neurological disorders accounted for 19% of the cases. This included one patient with functional convergence spasm, two patients with functional spasmodic dysphonia, two patients with fluctuating dysphagia and dysarthria and one with generalised fatigue.

The median age at symptom onset was 53 years and half were women. The median duration of symptoms to the false "MG" diagnosis was 0.5 years. The median duration on immunotherapies was only 1.6 months before the final diagnosis was made. However, one elderly patient was on immunotherapies for several years before she referred herself for a second opinion.

The initial MG diagnosis was based on the following clinical presentation; fluctuating ophthalmoplegia, dysphagia, dysphonia or dysarthria, non-fluctuating ptosis, and generalised fatigue or various combinations. One case was referred with ptosis and dysphonia, but on careful history taking this patient had ptosis due to tarsal dehiscence after cataract surgery and the dysphonia was associated with anxiety and panic.

In five patients given ChEI, only two had reported subjective positive responses. Only one patient had RNS which showed no decremental response whereas in the others the diagnosis was revisited in each based on the clinical features namely inconsistent symptoms and signs, distractibility, severe fatigue which started as the patient woke up and lasting the whole day, incongruent signs and symptoms, forced speech and the presence of Hoover's sign on examination.

At the time of final diagnosis of functional neurological symptoms an explanation of the condition was given to the patients and the distractibility of the signs showed and explained. All patients were started on antidepressants and referred to a neuropsychiatry service for cognitive behavioural therapy. Four improved on follow up and was discharged. One patient was lost to follow up and another patient's symptoms had remained the same but did not worsen after stopping the immunotherapy.

D. Motor neuron disease was also a common cause of a false positive MG diagnosis in our cohort**.** Six patients were identified: 1 progressive bulbar palsy (PBP), 1 progressive muscular atrophy (PMA), 1 primary lateral sclerosis (PLS) and 3 amyotrophic lateral sclerosis (ALS). The median age at symptoms onset was 63 years and ranged between 56 and 69. The median duration of immunotherapies to the false diagnosis of MG was 4 months. The median age at final diagnosis was 64 years.

Four patients in this group presented with bulbar symptoms and an element of fatigability in their limb weakness. One patient presented with dysphagia and dysarthria only and another patient had only limb weakness. Three of these patients experienced subjective improvement on neostigmine and/or oral pyridostigmine and three patients had objective positive response to ChEI and one patient even had resolution of dysphagia on pyridostigmine for <3 months. Of interest was the clear objective improvement in dysphagia and proximal weakness in 2 patients after the neostigmine test. However, these improvements disappeared within a few weeks and symptoms of spasticity became increasingly prominent.

RNS was done only in two patients and showed borderline decremental response of 8.8% and 5%.

Clues that led to the final diagnosis were progression of symptoms over time. Spasticity became increasingly evident as the disease progressed. A patient who was diagnosed with PMA after six months of being on immunotherapies had previous tongue cancer which was resected 3 years prior to presentation adding to the diagnostic difficulty, as well as poorly controlled diabetes mellitus. Overall, the MND patients were diagnosed as such within 4 months of being on an incorrect therapy.

E. Muscular dystrophy All four cases with muscular dystrophy presented with slowly progressive ptosis and ophthalmoplegia, followed by dysphagia, dysarthria and mild proximal muscle weakness. The median age at onset was 58 years with median duration of symptoms prior to presentation of 2 years. These cases included: 3 probable oculopharyngeal muscular dystrophy (OPMD) and 1 myotonic dystrophy 1 (DM1) which was confirmed with molecular genetic testing. Two of the patients (one OPMD and one DM1) presented in respiratory failure requiring intubation and mechanical ventilation. The patient with DM1 was also known with chronic obstructive lung disease and a superimposed pneumonia which triggered the respiratory distress.

The prior diagnosis of "MG" was based on a partial response to ChEI measured by increase in vital capacity of >300mls compared to baseline in two patients who presented with respiratory failure. Both remained on invasive ventilation and subsequently received IVIG without a response. The other two patients had negative responses to ChEI but the clinical symptom complex which included ptosis and bulbar symptoms resulted in a transient treatment course of CHEI and steroids. All four cases were only subjected to immunotherapies for a median time of 2 months.

The clues that led to the final diagnosis were failure to wean the two patients off the ventilator, the revelation of an autosomal dominant family history in 2 of the patients, one with myotonic dystrophy 1 and one with oculopharyngeal muscular dystrophy. The patient with DM 1 had frontal balding, a long thin face with severe facial weakness, and family photos of the patient confirmed the long-standing symptoms and genetic testing confirmed a trinucleotide expansion in the DMPK gene. The three patients with OPMD were not molecularly confirmed, due to the absence of appropriate testing in this country, but rather a presumptive diagnosis was made based on dystrophic features on muscle biopsy in the context of the phenotype. One of these had a sister who was diagnosed with OPMD at another institution, also based on clinical and histological criteria.

F: **Other diagnostic categories**

One patient with a final diagnosis of progressive supranuclear gaze palsy (PSP) had a subjective response to ChEI. This patient was a 70 year old female who presented with fatigable weakness and dysphagia for two years. Later, there was an insidious onset of ophthalmoplegia, ptosis, dysphagia, dysarthria and within months the ataxia of gait became obvious clinically. The initial RNS showed a decremental response of >10% in the right facial nerve, although it was not reproducible. Based on her symptomatic, albeit largely subjective response to pyridostigmine, prednisone and methotrexate was started. Within 2-3 months it became clear that there was no improvement and the clinical picture was progressing with the development of ataxia and postural instability. The immunotherapy was discontinued.

A 44 year old male known with relapsing multiple sclerosis presented with subacute ptosis in addition to partial internuclear ophthalmoplegia. An additional diagnosis of MG was entertained for a few weeks when the brainstem MRI did not show an appropriate lesion and pyridostigmine produced a subjective response. However, after one month on pyridostigmine

with no response, a decision was made to treat the patient with methyl prednisone intravenously and the symptoms resolved and a brainstem MS relapse was made.

Table 1: **Baseline characteristics, investigations and treatment of cases who were first treated as MG by final diagnosis**,

	CMS n=10	**Mito n=3**	**FuD n=6**	**MND n=6**	**MD n=4**	**PSP n=1**	**MS n=1**
AAO, median (IQR)	10 (6-20)	18 (16-19)	53 (39-54)	63 (56-69)	58 (53-64)	68	44
AAF, median (IQR)	26 (14-57)	41 (34-47)	53 (39-57)	64 (59-72)	61 (55-67)	70	44
Sex: female, n (%)	6 (60)	3 (100)	3 (50)	5 (83)	2 (50)	1	0
Symptoms to "MG" dx, yrs, median (IQR)	8 (3-10)	3 (3-21)	0.5(0.3-0.9)	0.3(0.3-2.7)	2(1.6-2.1)	2	0.1
Duration of "MG" dx, months, median (IQR)	45 (13-153)	48 (25-150)	1.6(1.2-2.3)	4 (2.5-5)	2(1-53)	3	1
CHEI (oral/IMI), n (%)							
Objective +ve	6 (60)	2(66)		3(50)	2(50)		
Subjectively +ve		1(33)	2 (33)	3(50)		1	1
Negative	4 (40)		3 (50)		2(50)		
RNS (3Hz): n (%)							
>10% decrement	4 (40)†	1*			ND	1*	ND
7-10% decrement	1 (10)			1*			
<7% decrement	3 (30)	1	1	2			
Treatment for MG: n							
Pyrid	2	1	1				1
Pyrid, pred	4		2	1			
Pyrid, pred, AZA/MTX	2	1	3	3	2	1	
PLEX/IVIG				1‡	2‡		
CTX,IVIG/PLEX	1‡			1‡			
IVIG, thymectomy	1‡	1‡					

CMS: congenital myasthenic syndromes, Mito: mitochondrial cytopathies, FuD: functional disorder, MND: motor neuron disease, MD: muscular dystrophy, PSP: progressive supranuclear palsy, MS: multiple sclerosis

AAO: age at onset in years, AAF: age at final diagnosis in years, IQR: interquartile range, dx: diagnosis, yrs: years, ChEI: cholinesterase inhibitors, RNS: repetitive nerve stimulation

Pyrid: pyridostigmine, pred: prednisone, AZA: azathioprine, MTX: methotrexate, PLEX: plasma exchange, CTX: cyclophosphamide, IVIg: intravenous immunoglobulin, CBT: cognitive behavioural therapy

†RNS decremental response reproducible, *RNS decremental response non reproducible, "MG": false MG diagnosis, ND not done, ‡ in addition to AZA/MTX, pyridostigmine, prednisone

Table 2: Summary of the initial clinical presentation and clues that led to the final diagnosis

MG mimics by Final diagnosis	Clinical presentation	Clues to final diagnosis
Probable CMS	Fatigable ptosis; Ptosis, ophthalmoplegia & fatigable limb weakness; Ptosis & bulbar; Ptosis & fatigable limb weakness	Childhood onset, positive family history & no response to immune therapies
Mitochondrial cytopathies	Ptosis, ophthalmoplegia, bulbar and mild proximal muscle weakness	Long duration of symptoms with progression & no response to immunotherapy
Functional neurological disorder	Fluctuating ophthalmoplegia, dysphonia, dysarthria, generalised fatigue symptoms, fluctuating swallowing difficulty	Disconnect between symptoms and signs, distractible, depression, fatigue & anxiety
Motor neuron disease	Bulbar with transient improvement on pyridostigmine, fatigable weakness	Progression of symptoms over weeks
Muscular dystrophy	Ptosis, ophthalmoplegia, dysphagia, proximal weakness & additional respiratory failure	Failure to wean off ventilator, Positive family history, no response to immune therapy
Progressive supranuclear palsy	Fatigable ptosis, ophthalmoplegia, limb weakness	Progression of symptoms to dementia, parkinsonism, ataxia
Multiple sclerosis	Ptosis & internuclear ophthalmoplegia	Known with MS, symptoms resolved after methyl prednisone pulse

Discussion

Here we present 31 cases collected over a 20 year period who were initially treated as MG for varying periods before the diagnosis was corrected. Our findings are similar to other reports. As expected, the cases with probable CMS contributed to majority of the cases mimicking autoimmune MG. Therefore, neurologists should be aware of the possibility of CMS as a diagnosis particularly in children presenting with a myasthenic syndrome. These patients will improve on cholinesterase therapies, but do not need immune therapies in addition. The second most frequent misdiagnosis was functional weakness. Although some of the MG mimics were also 'misdiagnosed' by our clinic, they were consistently detected earlier compared to the patients who were referred from elsewhere (data not shown). This does highlight the importance of referring patients who are not "responding to therapy" to a specialist centre. Below we briefly discuss the main features.

Congenital myasthenic syndrome is a rare group of inherited disorders that result in defects of neuromuscular transmission.[27, 31] Onset is typically after birth or early childhood, but late onset has been described.[27] The clinical presentation includes fatigable weakness of extraocular muscles with or without ptosis that evolve slowly and episodes of respiratory

crises that may improve over time.[31] Other symptoms include feeding difficulties, hypotonia, weakness, arthrogryposis, progressive respiratory difficulties in the neonate, and delayed motor development.[31,32] However the latter symptoms are not specific for CMS in the neonate and can be similar to congenital myopathy.[31,32] Autosomal recessive inheritance pattern is the most common pattern hence the absence of family history in the majority of the patients.[27] CMS is heterogeneous in presentation, therefore posing diagnostic and management challenges, especially in children.[31] A high index of suspicion is required to make the diagnosis. One of the limitations of our results was that we only consulted with patients as adults and the onset of symptoms was estimated by history and recall.

Ptosis in childhood, is a frequent symptom and sign in CMS.[31] It is also important to recognize that CMS can present in adulthood. Ptosis may be unnoticed until adulthood, because of slow and insidious progression, and therefore reviewing old photographs can be useful (also in mitochondrial cytopathies- see below). Abichat et al, described the largest cohort of 680 patients with probable or definite CMS, of whom 92% had childhood onset and the remainder only manifested between 20 -50 years of age.[32]

One of our elderly CMS cases we suspect had false positive AChR antibodies which can be found in this age group.[33] Vincent et al, found false positive AChR in <1% of 1147 elderly patients aged ≥ 75 years.[34]

A positive family history is another important diagnostic clue towards CMS. However the absence of family history does not exclude the diagnosis, because majority of cases are autosomal recessive. Parental consanguinity should be questioned as it increases the likelihood of autosomal recessive conditions.[27,31,32] A limitation of this work is that we have not been able to confirm the molecular mutations in our CMS cases to date due to lack of resources. Nevertheless, a diagnosis of CMS can be made based on the clinical presentation of fatigable symptoms with either positive repetitive nerve stimulation and/or a response to a trial of pyridostigmine, and the absence of autoantibodies, a family history, childhood onset, absent response to immune therapy in selected cases. Although these were the same criteria used to diagnose CMS by others, [31] in about 30 to 50% of cases, a genetic mutation could not yet be identified.[32] Importantly, a small numbers of cases with autoimmune myasthenia gravis may have positive family history of this condition as well. However, this does a have a more complex “inheritance” and is not always confined to first degree relatives.[35]

Chronic progressive external ophthalmoplegia (CPEO) is one of the most common mitochondrial cytopathies.[36] The molecular defect in most of the cases is a single large-scale mtDNA deletion and majority number of cases are sporadic.[36] Therefore, the risk of recurrence is very low in offspring of affected mother and non-existence in offspring of affected father.[13,36] About 15% of CPEO cases have an autosomal dominant/recessive inheritance pattern due to a mutation in the nuclear DNA genome.[13,36] CPEO is characterised by ptosis and ophthalmoplegia and is frequently symmetrical therefore individuals seldom complain of diplopia.[36] In our series cases had either unilateral ptosis at symptom onset or mild fatigability which are unusual features and may have caused diagnostic uncertainty and may be confused with MG which usually presents with asymmetrical ptosis.[37] Although these

features have been described as case reports it is unclear how frequently this occurs in larger cohorts of CPEO.[37,38]

About 90% of patients have additional facial, bulbar or limb muscle weakness. Many patients may also have multisystem involvement such as hearing loss, ataxia and diabetes and that is when they are classified as "CPEO plus".[36] Although it is expected to run a benign course[13], 2 of the 3 cases in this cohort developed progressive symptoms of bulbar and limb weakness in mid-life. The diagnosis of mitochondrial cytopathy is made via a muscle biopsy for histochemical analysis and the biochemical analysis of the respiratory chain enzyme.[39] Red ragged fibers and cytochrome c oxidase (COX) negative fibers are the most common findings in mtDNA deletion diorders.[39] Detection of the molecular defect of a single-large mtDNA deletion confirms the diagnosis. This can be done in blood lymphocytes or muscle biopsy. In children mtDNA is easily detectable in blood, but not in adults.[39] This is because of increasing amounts of deleted mtDNA molecules are selectively depleted from the rapidly dividing leucocytes with age.[39-41] As an example, the patient aged 45 had a muscle biopsy which only showed scattered COX-negative fibers, which is not diagnostic, and the mtDNA deletion screen was negative in the blood lymphocytes. A mtDNA deletion was eventually confirmed from the mtDNA extracted from the muscle tissue based on a high index of suspicion.

The diagnosis of a functional neurological disorder is made in a patient presenting with symptoms out of keeping with signs, physical symptoms which fluctuate during the examination, or change when the patient is distracted.[42,43] Functional neurological symptoms are not uncommon; Stone et al. reviewed the diagnoses of 3781 new referrals to a neurology clinic in the UK and found 14% of cases were diagnosed with functional neurological disorders.[44] It is important to recognize that not all patients have psychogenic risk factors.[44] Neurologists make the diagnosis based on a careful history taking and neurological examination, as well as identifying positive clinical findings such as Hoover's and the features mentioned above.[44]

In this cohort most of the patients in the functional category presented with speech and swallowing problems in addition to symptoms of fatigue. Interestingly one of the patients presented with fluctuating ocular symptoms which was recognised as functional convergence spasm by the second visit. This is a classical although rare functional syndrome. In 2012, Fekete et al, reported that of their 13 cases with convergence spasm, 69% were functional.[45] Two of our patients had functional dysphonia. Similarly, to other functional disorders, the variability of the voice is often the clue. As the patient is distracted and speaks, the voice returns to normal. In this setting further examination is often not required. Pseudodystonic speech may require additional examinations such as laryngeal examinations.[46] The diagnosis is often not easy at the beginning, but sudden onset of voice change/loss of voice and fluctuating nature in the presence of depression and anxiety should point towards the diagnosis of functional dysphonia in the absence an alternative diagnosis.[46] However, isolated laryngeal MG presenting with dysphonia has been described [47,48] and dysphagia is a common symptom in MG and may also be isolated.[49]

Although the presence of depression and anxiety symptoms are not prerequisites for making a diagnosis of functional symptoms, taken together with features described above such as

distractibility and changing symptoms with poor responses to therapy should raise a possibility of functional disorder. However, functional syndromes are not diagnostic categories of exclusion and should be diagnosed on the basis of an appropriate history and clinical examination findings.

MG and MND/ALS (used interchangeably) are both neuromuscular diseases that have a different pathophysiology, but occasionally share some clinical features such as bulbar symptoms, motor weakness and brisk reflexes.[15] We had 6 patients with the final diagnosis of MND/ALS who were initially misdiagnosed as MG in our cohort largely due to either subjective or objective transient responses to ChEI. While the response in MG is sustained, in ALS the response is short-lived and wears off as we have seen in our patients.[15] Two of our patients showed a borderline and non-reproducible decremental CMAP on RNS which has been reported by several authors[50,51] and not infrequently. For example, almost 50% of 192 patients showed a decremental response on RNS and 56 had definite CMAP decrement with a mean of 17% and another 44 had a borderline decremental response with a mean of 7% .[51] These findings were reproducible and their conclusion was that the decremental response in ALS indicates functional alteration at neuromuscular junction likely due to nascent units trying to re-innervate the endplates.[51]

Although the fatigue in ALS is more generalised, muscle fatigability, albeit transient, has been observed in ALS.[15] There are case reports, similar to ours, where the diagnosis of MG was made based on a subjective response to ChEI which disappeared with a few weeks and the diagnosis of ALS was evident. In one case a patient also had a false positive SFEMG result and together with 4 month history of head drop and shortness of breath on exertion and an initial effect of pyridostigmine, a false diagnosis of MG was made.[15]

False positive AChR-Abs have also been described in some cases of patients with ALS/MND and even with very high titres.[52,53] AChR-Ab might have been falsely positive as discussed above (Vincent et al), although the authors speculated that the elevation of these antibodies may have been due to response to degeneration of the AChR at the neuromuscular junction.[52,53]. Rarely, cases of MG overlap with ALS have been described, and the occurrence may have been by chance.[54]

Some types of muscle dystrophy such as OPMD and MD can be confused with MG because they may have ptosis in addition to insidious involvement of the respiratory muscles which can suddenly decompensate due to factors such as pneumonia or surgery etc. These patients may therefore require ventilatory support and see a neurologist for the first time in ICU. In this setting they may be confused with a new, severe presentation of MG such as the cases we presented here. The initial diagnosis of MG was raised by the mild increase in their lung function after ChEI although these effects were transient. The take home message, albeit based on 2 cases, is that a small increase in the VC must be treated cautiously. However, because of the severity of the implications of non-responsiveness on a ventilator, it would be imperative in these isolated cases to treat the patient with at least one course of intravenous immune therapy.

Although the OPMD cases were not molecularly confirmed, the clinical presentation, muscle biopsy and family history were in keeping. There are a few case reports in literature of OPMD

that was misdiagnosed as MG. OPMD is more common in the French Canadian and Hispanic population, however an Afrikaner family with OPMD has also been reported.[55] Fujikura at el [56] described a case similar to ours of a 64 year patient who presented with slowly progressive bilateral ptosis and diplopia, dysphagia, dysarthria with diurnal variation over 10 years. The patient showed improvement on ChEI, but it was not sustained. After some time the dysphagia continued to deteriorate and genetic studies confirmed OPMD. These cases highlight the overlap in some clinical features between MG and OPMD and should alert the clinician that this condition is not only limited to a specific population. A report described the co-existence of OPMD with MG.[57] Both DM1 and OPMD are autosomal dominant and therefore reviewing the family history and family photograph albums may be informative There are several case reports in the literature of DM and MG with AChR-abs positive co-existing in one patient, [58-60] although the question of possible false positive AChR abs must be raised.

The diagnosis of parkinsonian disorders such as PSP and MSA is challenging and has been confused by many neurologists (Heckmann unpublished experience). In MG the frontalis muscle become chronically hypercontracted due to weakness of lid elevators.[15] Facial weakness that is often seen in MG may produce a "sagging" expression leading to loss of facial expression[15, 61] which is the hallmark for Parkinsonism and may be mistaken for facial weakness in MG. Frontalis muscle hyperactivity is commonly seen in PSP and may be mistaken for fatigable ptosis.[62] Dysphagia, dysarthria and head drop can also be seen in both MG and Parkinsonsims.[61] Although our case had a decremental response on RNS, it was not reproducible, highlighting the technical difficulties with performing RNS.

We had one case with MS, in whom we transiently entertained the possibility of MG. MG patients may have additional autoimmune disease most frequently thyroid disease. Systemic lupus sclerosis may co-occur with MG and other autoimmune disease.[63] The patient claimed a partial response to ChEI but it soon became clear that he required a pulse intravenous of methylprednisolone (IVMP) for MS relapse and he improved. IVMP is usually not given in MG because it may worsen the symptoms initially. Although, other case reports refer to structure disease as a mimic of MG, this was not identified in this cohort.

The limitation of this case series is that, although the clinical information was captured observationally over 20 years, some of the information was incomplete. In addition, the largest group of probable CMS and OPMD, were not molecularly confirmed by genetic testing as these tests are not presently available in this country. In about 26% of patients, the prior MG diagnosis was based on subjective responses to CHEI. In some patients (data not shown), the MG diagnosis was made by other neurologists elsewhere and when they were reviewed at our centre due to poor responsiveness, the diagnosis was changed immediately. However, the aim of the study was not to identify the source of errors but to highlight the clues for errors. Also, we need to acknowledge that this is a single centre experience. Perhaps a questionnaire study design may be considered in the future to identify reasons for misdiagnosing MG.

Conclusion

MG is an immune mediated neuromuscular disorder which can present heterogeneously. The hallmark for this condition is fatigable weakness of selective muscles. The two commonest mimics were conditions with inherited forms of myasthenia and those in whom there is prominent symptoms of fatigue but without any evidence of fatigable weakness. Other important take home messages are that early ALS may show fatigable weakness and responsiveness to acetylcholine esterase inhibitors although only transiently. Furthermore, that mitochondrial myopathies may have asymmetrical onset of ptosis. Functional patients do better with cognitive behavioural therapy if identified early. AChR-Abs can be falsely positive, especially in ALS and elderly patients. A reproducible decremental response on RNS does not always confirm or support a clinical diagnosis of MG and is not excluded if it is negative. A positive RNS may also be seen in other neuromuscular diseases. However technical limitations should be taken into account. Finally, this report is not to highlight how many times the diagnosis of MG was wrong, but that treatment unresponsiveness should raise a possibility of an alternative diagnosis, review of therapies and/or referral for to a centre of expertise.

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